

A Brief History of Antibiotic Development & Resistance

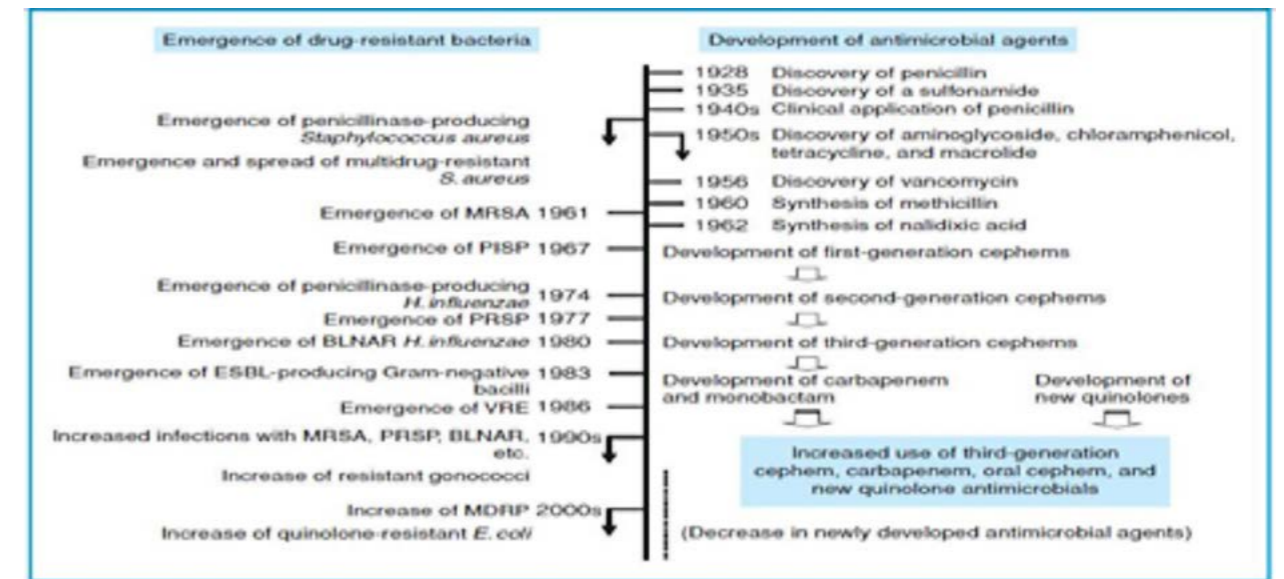


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antibiotics represented a key medical milestone in the 20th century. The word antibiotic stems from “anti” meaning against and “biota” meaning life. Therefore, by definition, antibiotic translates into “anti-life”.

The first antibiotic ‘penicillin’ was discovered in the year 1929 by Sir Alexander Fleming. He discovered that an agar plate that has the bacterium staphylococci on it got contaminated by a *Penicillium* mold. This mold, which has formed a zone around the *Staphylococcus*, was of interest to Fleming as he was searching for potential antibacterial compounds. Fleming was interested in this observation and he did several experiments to prove that culture broth of the mold had prevented the growth of the *Staphylococcus* even after being diluted up to 8,000 times. After many years, Ernst Chain and Howard Florey were able to develop a way

An antimicrobial agent or an antibiotic is defined as an agent produced naturally by an organism or prepared synthetically that damages or stops the growth of microbes such as bacteria, fungi, or protozoa. The discovery of



Trend of development of antimicrobial agents and emergence of drug-resistant bacteria

Figure 1: Trend of development of antimicrobial agents

to isolate penicillin which has been used to treat bacterial infections during World War II. Penicillin was introduced to clinical use in 1946 where it made a significant effect on public health. The discovery of penicillin was a milestone for public health because it reduced the spread of disease. During World War II, there was a high demand for the production of antibiotics to fight off infections. Big pharmaceutical companies such as Lederle, Parke-Davis, and Pfizer began seeking for alternatives to penicillin, with wider therapeutic use. Lederle was the first company to offer the antibiotic Aureomycin for sale in December 1948 where it was known as the most versatile antibiotic yet discovered, with a wider range of activity than other known therapies.

Other pharmaceutical companies created their own broad-spectrum antibiotics. Pfizer was able to alter the marketing of antibiotics with the production of Terramycin in 1950. Other antibiotics were discovered as time went on, including streptomycin, chloramphenicol, and tetracycline with an effective activity on a full array of bacterial pathogens. As antibiotics became more popular, the demand for antibiotics also increased. Antibiotic output and prescribing as a whole was monumental. The consumption of antibiotics in the United States grew; between the years 1950 and 1956, consumption increased from 139.8 to 645.2 metric tons. During that time, the healthcare industry and the role of antibiotics were proven to be growing and

contributing greatly to the care of patients. Antibiotics not only fought infections which were fatal to many people, but also gave hope to those who were ill, or those who had family members that were ill. Generally, as antibiotics were becoming popular, the demand on them started to increase. As a result, new antibiotics were created to meet the needs. For example, the development of semi-synthetic penicillin and the introduction of methicillin and ampicillin occurred due to the isolation of 6-aminopenicillanic acid. In addition, new generations of penicillin or broad spectrum penicillin were developed to fight other forms of bacterial infections. Eventually, this need has been a principal reason to induce the creation of other forms of penicillins, which in turn led to the finding of the second generation penicillins, Ampicillin and Amoxicillin.

On another hand, the emergence of resistant bacteria with their abilities to mutate has surpassed our imagination. In some cases, antimicrobial agents that were previously useful are no longer effective. The history of resistant bacteria is outlined in (Figure 1).

Staphylococcus aureus (*S. Aureus*) is a gram positive bacterium that is frequently isolated in clinical settings. It was observed that this organism has rapidly acquired resistance to sulphonamides. *S. aureus* was sensitive against the antibiotic penicillin in the early stages, however, in 1960s, when strains were observed to produce penicillinase,

methicillin-resistant *S. aureus* (MRSA) was isolated. Nowadays, MRSA is a global concern as it is associated with nosocomial infections and leading to mortalities in some cases. At that time, new antibiotics, including second and third generation cephalosporins, were broadly introduced and used. In a Japanese study, MRSA seemed to be sensitive and responded to glycopeptide antibiotics such as vancomycin. However, during the 1990s, vancomycin-intermediate *S. aureus* (VISA) was reported in the country. It was speculated that the thickening of the bacterial cell wall is correlated with the decreased sensitivity towards this drug. Then again, vancomycin-resistant *S. aureus* (VRSA) that was reported in the US seemed to have acquired the resistance genes horizontally from vancomycin-resistant enterococci (VRE).

Concerning *S. pneumonia*, the strain was initially sensitive to penicillin but it started acquiring resistance in the mid of 1960s. Penicillin-intermediate *S. pneumonia* (PISP) strains were isolated at that time and penicillin-resistant *S. pneumonia* (PRSP) strains appeared in the 1970s. The use/misuse of oral cephalosporins antibiotics seems to be contributing to the increase in PRSP. In addition, a remarkable increase in macrolide resistance in this species was also observed, which seems to be correlated with the

use of macrolides in the country. In 1980s, B-lactamase producers in these species were isolated and resistant to ampicillin. It has been shown (Figure 2) that the number of B-lactamase enzymes producers is increasing throughout the years.

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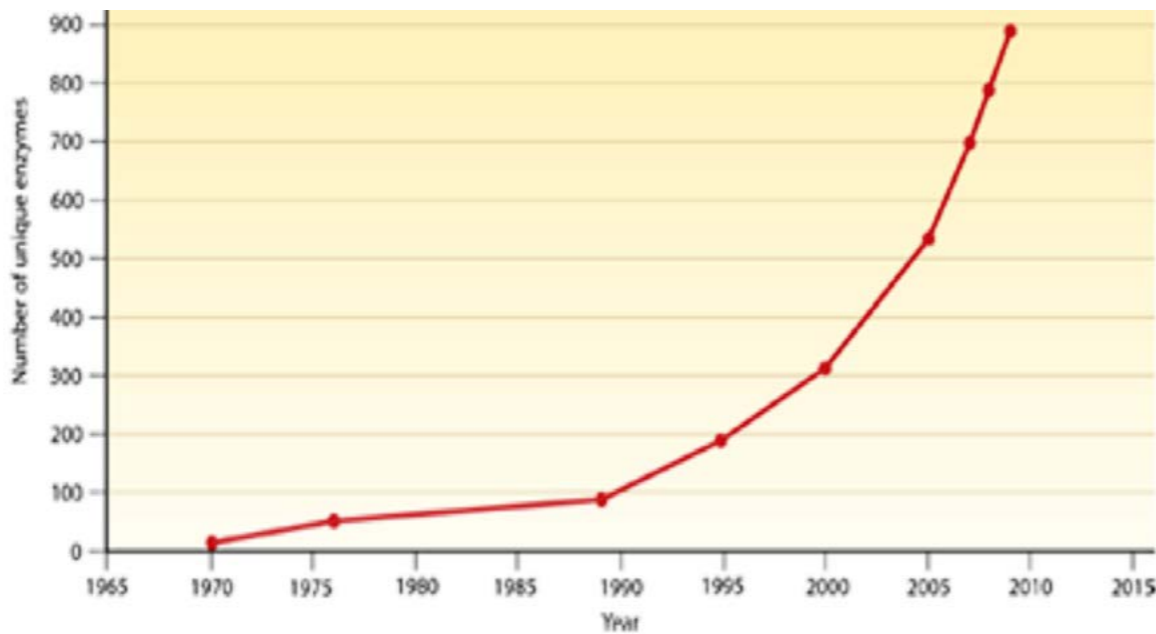
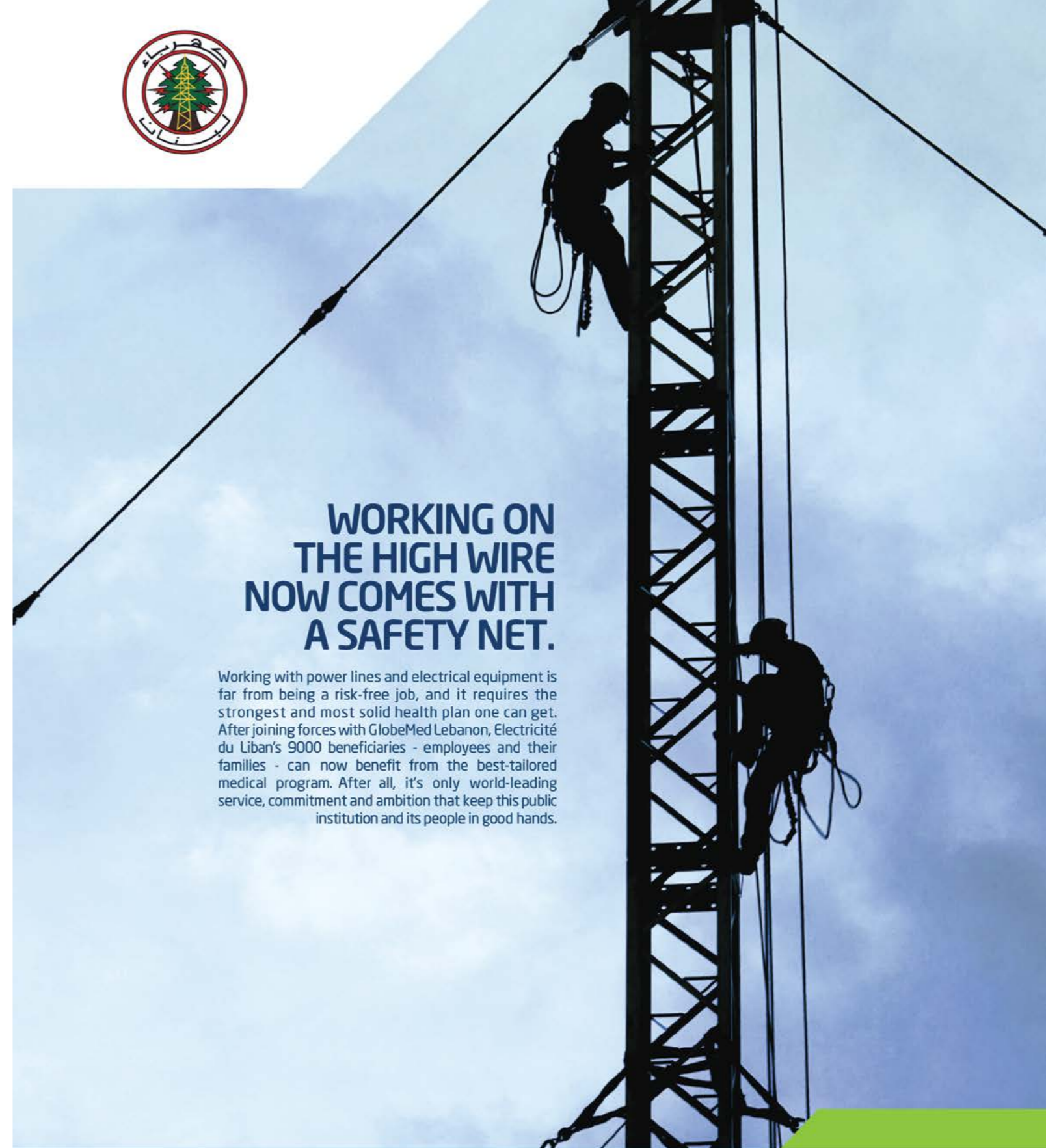


Figure 2: Number of unique B-lactamase enzymes identified since the introduction of the first B-lactam antibiotic.



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